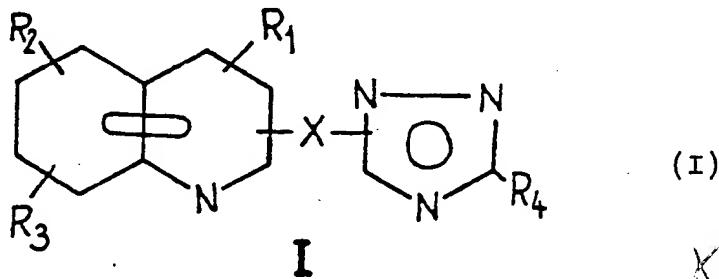


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(71) Applicant (for all designated States except US): ALKALOIDA VEGYÉSZETI GYÁR [HU/HU]; Pf. 1., H-4440 Tiszavasvári (HU).		Published With international search report.
(72) Inventors; and		
(75) Inventors/Applicants (for US only): KÓRÓDI, Ferenc [HU/HU]; 9, Elmunkás u., H-4440 Tiszavasvári (HU). FRANK, László [HU/HU]; 23.d, Elmunkás u., H-4440 Tiszavasvári (HU). SALAMON, Zoltán [HU/HU]; 17-19.b, Kabay János u., H-4440 Tiszavasvári (HU). SÁNDOR, József [HU/HU]; 8., Jókai u., H-4450 Tiszalök (HU). POCSAI, Emma [HU/HU]; 17-19.a, Kabay János u.,		

## (54) Title: TRIAZOLYL QUINOLINE DERIVATIVES



## (57) Abstract

New triazolyl quinoline derivatives and acid addition salts thereof (wherein R<sup>1</sup> stands for hydrogen, methyl, trihalogenomethyl or carboxy; R<sup>2</sup> is hydrogen, halogen, C<sub>1-4</sub> alkyl, hydroxy, C<sub>1-4</sub> alkoxy, phenoxy, amino, acetamino, C<sub>1-4</sub> dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl; R<sup>3</sup> represents hydrogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy; R<sup>4</sup> stands for hydrogen, methyl or ethyl and X stands for a valency bond or -S-) The new compounds of general formula (I) possess valuable analgesic, antiphlogistic and fungicidal effect and can be used both in therapy and agriculture.

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## TRIAZOLYL QUINOLINE DERIVATIVES

This invention relates to new triazolyl  
 5 quinoline derivatives, a process for the preparation thereof and pharmaceutical and fungicidal compositions containing the same.

According to an aspect of the present invention there are provided new triazolyl quinoline  
 10 derivatives and acid addition salts thereof  
 (wherein

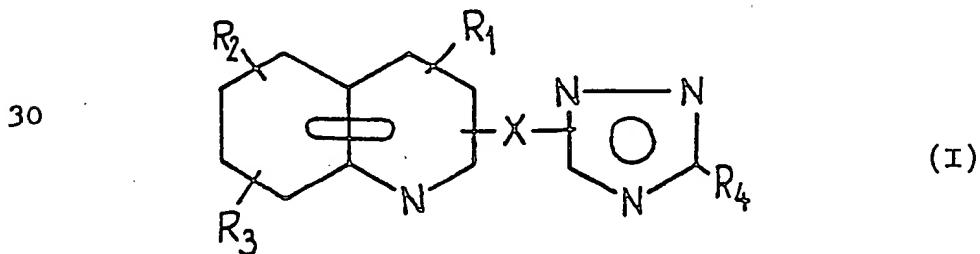
$R^1$  stands for hydrogen, methyl, trihalogeno-methyl or carboxy;

15  $R^2$  is hydrogen, halogen,  $C_{1-4}$  alkyl, hydroxy,  $C_{1-4}$  alkoxy, phenoxy, amino, acetamino,  $C_{1-4}$  dialkylamino, acetyl, benzoyl, methylthio, carboxy, cyano, ethoxycarbonyl, nitro or trihalogenomethyl;

20  $R^3$  represents hydrogen,  $C_{1-4}$  alkyl or  $C_{1-4}$  alkoxy;

$R^4$  stands for hydrogen, methyl or ethyl and  
 X stands for a valency bond or  $-S-$ )

According to a further aspect of the present invention there is provided a process for  
 25 the preparation of compounds of the general Formula  
 (I)



35 (wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and X are as stated above)

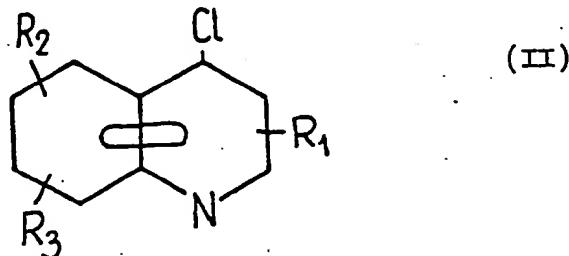
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and acid addition salts thereof which comprises reacting a halogeno quinoline derivative of the general formula (II)

5

10



or (III)

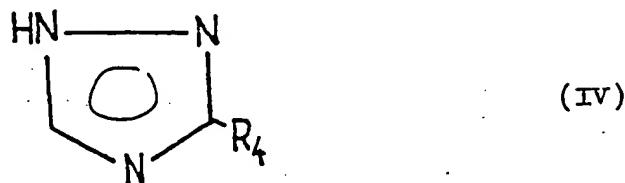
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(wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as stated above) with a 1,2,4-triazole of the general Formula (IV)

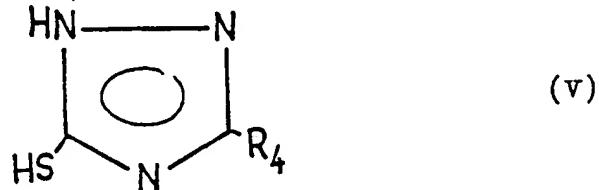
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30 or (V)

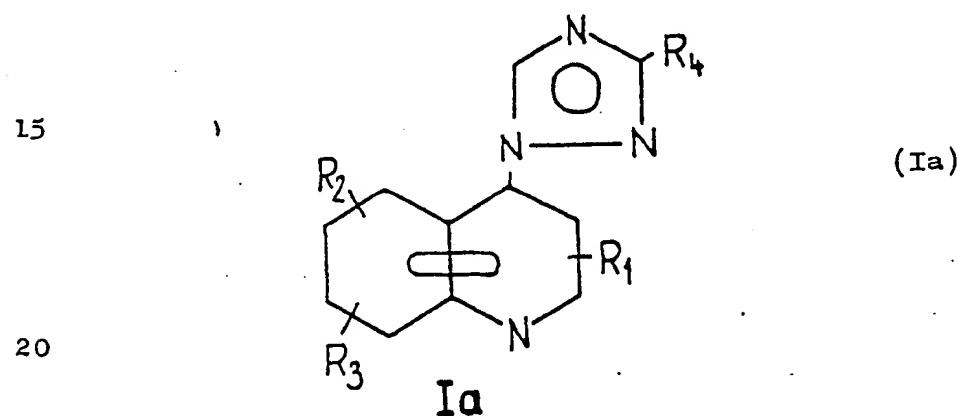
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(wherein  $R^4$  is as stated above) in the presence or absence of a solvent, in the presence or absence of an acid or a base, at a temperature between 0  $^{\circ}\text{C}$  and 200  $^{\circ}\text{C}$  and if desired isolating the product thus obtained in the form of the free base or an acid addition salt thereof.

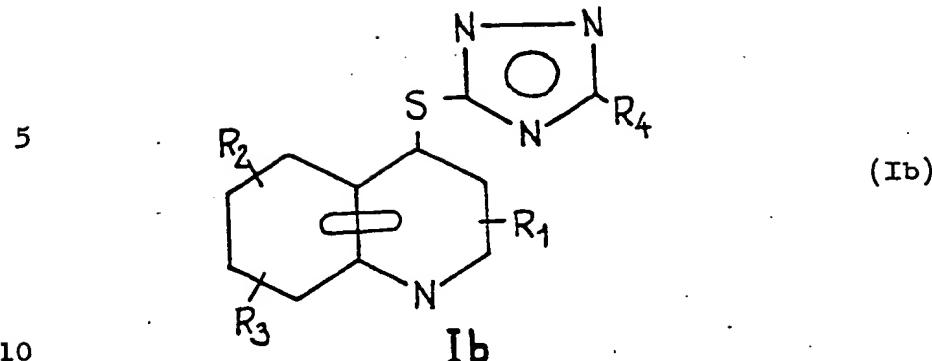
According to a feature of the process of the present invention there is provided a process for the preparation of compounds of the general 10 Formula (Ia)



which comprises reacting a 4-chloro-quinoline derivative of the general formula (II) with a 25 1,2,4-triazole of the general Formula (IV) (wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as stated above).

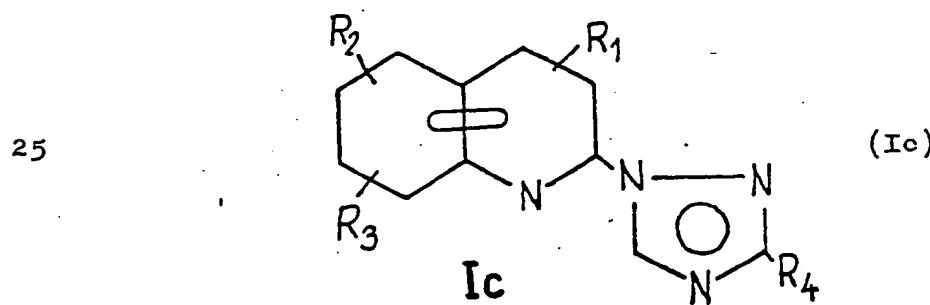
According to a further feature of the process of the present invention there is provided a process for the preparation of compounds of the 30 general Formula (Ib)

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which comprises reacting a 4-chloro-quinoline derivative of the general Formula (II) with a 3-mercaptop-1,2,4-triazole of the general Formula 15 (V) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated above).

According to a still further feature of the process of the present invention there is provided a process for the preparation of compounds 20 of the general Formula (Ic)

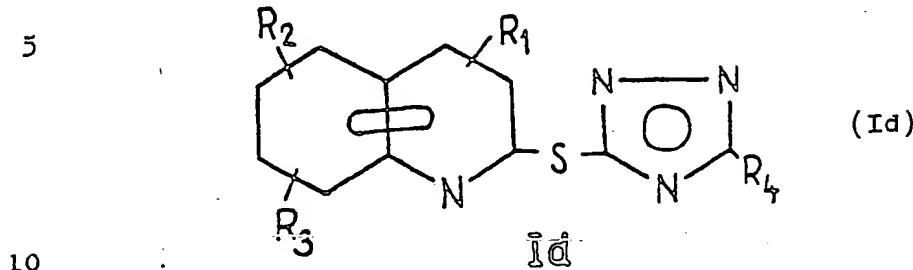


30 which comprises reacting a 2-chloro-quinoline of the general Formula (III) with a 1,2,4-triazole of the general Formula (IV) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated above).

According to a still further feature of 35 the process of the present invention there is

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provided a process for the preparation of compounds of the general Formula (Id)



which comprises reacting a 2-chloro-quinoline derivative of the general Formula (III) with a 3-mercaptop-1,2,4-triazole of the general Formula (V) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated above).

The starting materials used in the process of the present invention are known compounds. The prior art references of the starting materials are as follows:

20 4-chloro-quinolines of the general Formula (II): "The Chemistry of Heterocyclic Compounds" Vol. 32 Quinolines Part I pages 391 - 398; the references cited therein; Hungarian patent applications Ser. No. 3869/82 and 4003/82.

25 2-chloro-quinolines of the general Formula (III): "The Chemistry of Heterocyclic Compounds" Vol. 32 Quinolines Part I pages 387-390: J. Chem. Soc. P.I. 1981 1(5) 1537-1543.

30 3(5)-mercaptop-1,2,4-triazoles of the general Formula (IV): Hungarian patent application Ser. No. 4370/83; DOS No. 2,802,491; Chem. Ber. 1968, 101 (6) 2033-2036.

35 3(5)-mercaptop-1,2,4-triazoles of the general Formula (V): Liebigs. Ann. Chem. 637, 133 135-165 (1960).

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The new compounds of the general Formula (I) possess valuable biological properties and exhibit useful analgesic and antiphlogistic effect. Some representatives of the compounds of 5 the general Formula (I) are highly active against phytopathogenic fungal pests according to both in vivo and in vitro tests.

It has been found that the reaction 10 between 4- and 2-chloro-quinoline derivatives of the general Formula (II) or (III), respectively, comprising only electron repulsing substituents (e.g. methyl or methoxy groups) and 1H-1,2,4-triazoles or 3(5)-mercapto-1H-1,2,4-triazoles of 15 the general Formula (IV) or (V), respectively, is autocatalytic whereby the hydrochloric acid formed in the course of the reaction acts as catalyst. The reaction can also be catalysed by other acids, particularly strong mineral or organic acids or 20 acidic salts (e.g. sulfuric acid, trifluoroacetic acid or ammonium chloride). It is preferred to carry out the reaction in the presence of the said acidic compounds - particularly hydrochloric acid - which can be used in the range of from catalytic 25 to stoichiometrical amount.

If less basic chloro-quinolines comprising 30 electron attracting group or groups (e.g. chlorine, trifluoromethyl) are used, such catalysis is not observed. In this case, however, the reaction may be facilitated by carrying out the same in the presence of an organic or inorganic base (e.g. triethyl amine, potassium carbonate or sodium 35 hydroxide) used in stoichiometrical or higher amount. This pertains also to the case if the 1H-1,2,4-triazole or 3(5)-mercapto-1H-1,2,4-triazole

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derivative is used in the form of an alkali salt (e.g. sodium salt) thereof.

It has been found furtheron that the mercapto group is more reactive than the -NH-  
5 -group of the triazole ring.

The reaction (preparation of compounds of the general Formulae (Ia), (Ib), (Ic) and (Id)) may be carried out preferably in the presence of a polar organic solvent (e.g. ethanol, acetone,  
10 acetonitrile, dimethyl formamide, dimethyl sulfoxide etc). As reaction medium an apolar organic solvent (e.g. benzene, toluene, chloro benzene, dichloro benzene) may also be used and one may also work in the absence of an organic solvent in the  
15 melt.

The reaction of the present invention may be carried out at a temperature between 0 °C and 200 °C, preferably in the range of 20 - 150 °C. The reaction temperature is selected under taking  
20 into consideration the properties of the reactants and the method used.

It is sufficient to react the chloro quinoline component with a molar equivalent amount of the 1H-1,2,4-triazole or 3(5)-mercapto-1,2,4-triazole but the reactions generally take place more rapidly and completely if the starting material of the general Formula (IV) or (V) is used in a 1-2 molar equivalent amount.

According to a form the realization of the process of the present invention the reaction components are melt and the reaction having been terminated the product formed is isolated. According to the said embodiment of the process the product is formed in the form of the hydrochloride thereof. The direct reaction product is treated

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with an apolar organic solvent (e.g. ether, chloroform, benzene, hexane) or crystallized from a polar solvent (e.g. ethanol, methanol, acetonitrile, dimethyl formamide) or a mixture of polar and 5 apolar solvents.

The free base of the general Formula (I) may be isolated by cooling the reaction mixture, dissolving in water or a mixture of water and ethanol - preferably under adding a mineral or 10 organic acid - and precipitating the product by adding an organic or inorganic base. The crude product may be crystallized from a mixture of a polar organic solvent and water or polar and apolar organic solvents.

15 According to a further embodiment of the process of the present invention the reaction partners are reacted in the presence of an apolar organic solvent (e.g. benzene, toluene, xylene, hexane, carbon tetrachloride, chloro benzene, 20 dichloro benzene etc). The reaction having been completed the product precipitated in the form of the hydrochloride is filtered, if necessary crystallized and converted into the free base as described above.

25 According to a still further embodiment of the process of the present invention the reaction partners are reacted in a polar organic solvent (e.g. ethanol, ethylene glycol, acetonitrile, acetone, ethyl methyl ketone, dimethyl formamide, 30 dimethyl sulfoxide, glacial acetic acid). The product is isolated in the form of the free base or a salt formed with a mineral acid.

According to a preferred embodiment of the process of the present invention the reaction 35 is accomplished in a polar organic solvent (e.g.

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ethanol, ethylene glycol, acetonitrile, acetone, methyl ethyl ketone, dimethyl formamide), preferably in the presence of hydrochloric acid.

The acidic medium may be either provided 5 by introducing an acid (preferably hydrochloric acid) to the reaction mixture or by using the chloro quinoline component in the form of a salt (preferably hydrochloride) thereof. The product formed in the form of a salt may be isolated from 10 the reaction mixture according to one of the methods set forth above.

According to a further preferable form of realization of the present process of the invention the reaction is accomplished in a polar 15 organic solvent, in the presence of a molar equivalent or larger amount of a strong base (e.g. triethyl amine, potassium carbonate, sodium carbonate etc).

The above reaction may also be carried 20 out by using the triazole or mercapto triazole of the general Formula (IV) or (V), respectively, in the form of an alkali (e.g. sodium or potassium) salt thereof.

The structure of the new compounds prepared by the process of the present invention is 25 characterized and confirmed by means of NMR, IR and MS spectrum and the purity of the product is determined by thin layer, gas and liquid chromatography.

30 The compounds of the general Formula (I) possess valuable physiological properties and eliminate or efficiently relieve induced pain and inflammation processes. The significant advantage of the compounds of the general Formula (I) is 35 that in analgesic and antiphlogistic dose range

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ulcerative activity is observed not at all or but to a very small extent.

Thus the orally administered compounds of the general Formula (I) efficiently reduce 5 acute inflammatory processes. According to the method of Winter [Proc. Soc. Exp. Biol. Med. 111, 544 (1962)] carrageenin oedema is induced and evaluated on male Wistar rats fasted for 16 hours (body weight 160 - 180 g). Percental inhibition is 10 calculated from the average oedema values of the groups treated with the test compound on the one hand and with carrier (carboxy methyl cellulose, CMC; control) on the other. ED<sub>50</sub> values are 15 determined by means of regression analysis of the inhibition values. The test compounds are administered through a stomach canule in the form of a 1 % carboxy methyl cellulose (CMC) suspension, one hour before introducing the carrageenin injection. The carrageenin oedema inhibiting effect of 20 the test compounds are summarized in Table I.

The protecting effect of the test compounds against adjuvant induced arthritis is shown in Table II. According to the method of Newbold 0.1 ml of Freund complet adjuvant (Difco Lab. Mich. 25 USA) is injected to the plantar-surface of the right hind paw of male Wistar rats weighing 160 - - 200 g. The volume of the hind paws is measured before and 21 days after the administration of the adjuvant with the aid of a mercury plethysmometer. 30 The test compound is administered to the test animals for two weeks in a daily oral dose of 25 mg/kg. In Table II the "percental inhibition of the growth of paw volume" relates to the value determined on the 21st day.

35 In the adjuvant arthritis test, considered

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to be the best model test of rheumatoidal arthritis, the compounds of the present invention inhibit articular deformations more effectively than the reference substances Naproxen and Phenylbutazon.

5 The tests show furthermore that the compounds of the present invention are active not only in healing morphological deformations but effect in a desirable and useful manner the functional condition and fitness of the feet, moreover the general physical  
10 state and condition of the animals, too.

The analgesic effect of the compounds of the present invention is tested according to the hot (56 °C) plate test on male and female CFLP strain mice weighing 18 - 22 g. The point of time  
15 of the appearance of the deterring reaction (Abwehrreaktion) is determined and related to the latent time measured on the control group (Woolfe and McDonald 1944). At least 10 animals are used per dose. The test compounds are administered  
20 orally 60 minutes before the test in the form of a 1 % methyl cellulose suspension. The results are summarized in Table III. The test is carried out on separated male Wistar rats weighing 180 - 210 g and fasted for 16 hours. The test compounds are  
25 suspended in 1 % carboxy methyl cellulose and administered orally in a dose of 10 ml/kg.

Five hours after treatment the animals are sacrificed and their stomachs are placed into a 2.5 % formaline solution. The number and rate of  
30 punctiform haemorrhage and ulcers is evaluated according to the following scale:

0 = no lesion;  
1 = some punctiform haemorrhage (< 10);  
2 = diffuse haemorrhage or small ulcer (< 2 mm);  
35 3 = two or more minor small ulcer (< 2 mm);

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4 = one or more large ulcer (> 2 mm).

In a dose of 25 mg/kg and 100 mg/kg the compounds of the present invention do not 5 exhibit ulcerogenic effect. In acute test the UD<sub>50</sub> value of Naproxen and Indomethacin amounts to 20.8 mg/kg and 6.3 mg/kg p.o., respectively.

The acute toxicity of the compounds of the general Formula (I) is determined according 10 to the method of Litchfield - Wilcoxon on male and female rats of CFLP strain. The LD<sub>50</sub> values vary between 500 and 2000 mg/kg p.o.

According to a further aspect of the present invention there are provided pharmaceutical 15 compositions comprising in an effective amount at least one compound of the general Formula (I) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as stated above) or a pharmaceutically acceptable acid addition salt thereof as active ingredient in admixture 20 with suitable inert solid or liquid pharmaceutical carriers.

The pharmaceutical compositions may be prepared in a manner known per se by admixing at least one compound of the general Formula (I) or 25 a pharmaceutically acceptable acid addition salt thereof with suitable inert solid or liquid pharmaceutical carriers.

The compounds of the present invention may be used in therapy preferably for the treatment 30 of various rheumatic diseases, particularly rheumatoidal arthritis, spondylitis, osteoartrosis and gout. The active ingredient may be finished by known methods of pharmaceutical industry in forms suitable for enteral or parenteral administration (e.g. tablets, capsules, dragées, injec- 35

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tions etc.). The pharmaceutical compositions of the present invention may optionally comprise one or more further biologically active materials in addition to the compound of the general Formula 5 (I). The compositions comprise carriers and excipients generally used in therapy.

The dose of the compounds of the general Formula (I) varies between wide ranges and depends on several factors (e.g. body weight, age and condition of the patient etc.). The dose amounts 10 generally to 10 - 200 mg/kg body weight (enteral administration) and to 1 - 50 mg/kg (parenteral administration). The above ranges are, however, just of an informative character.

15 The compounds of the general Formula (I) possess considerable antifungal activity, too, and are active against phytopathogenic fungal strains and diseases. The compounds of the general Formula (I) are particularly effective against powdery 20 mildew. In Table IV the activity of some compounds of the general Formula (IV) against Erysiphe graminis f. sp. tritici strain are disclosed.

The following test method is used:  
Glasshouse conditions: temperature 20 °C; relative 25 humidity 80 %; strength of illumination 6000 lux. The test plants (MV-9 Autumn wheat) are cultivated in pots (diameter 20 cm) in a 1:1 mixture of sand and perlite. The average number of plants per pot amounts to 180, the height of the plants is 6-7 cm.  
30 About 8 ml of the aqueous suspension of the test compound is applied onto the plants with the aid of a sprayer.

The rate of infectedness is determined after 8 days. Activity is calculated from the 35 percental inhibition values. As control commercial

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products Fundazol 50 WP and Karathene LC 50 are used.

According to a further feature of the present invention there are provided fungicidal 5 compositions comprising as active ingredient in an effective amount at least one compound of the general Formula (I) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as stated above) or an acid addition salt thereof in admixture with suitable inert solid or liquid 10 carriers or diluents.

The said fungicidal compositions are prepared by methods known per se.

Table I

15 Antiphlogistic effect on carrageenin induced oedema on rats

	Test com- pound No.	Dose mg/kg p.o.	Percental inhibition of paw volume	ED <sub>50</sub> mg/kg p.o.
20	61	12.5	29	
		25.0	37	60.9
25	62	100.0	58	
		12.5	18	
30	62	25.0	51	
		50.0	59	38.4
	64	100.0	69	
		12.5	15	
		25.0	27	
		50.0	44	59.1
		100.0	65	

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Table I  
(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of paw volume	ED <sub>50</sub> mg/kg p.o.
69	12.5		27	
	25		33	
	50		52	35.0
	100		86	
74	12.5		26	
	25		55	25.7
	50		69	
83	12.5		21	
	25		63	
	50		70	28.1
	100		72	
107	12.5		29	
	25		40	
	50		70	30.6
	100		74	
108	12.5	10	19	
	25	10	45	
	50	10	61	38.5
	100	10	70	
110	12.5	10	10	
	25	10	42	
	50	10	46	51.4
	100	10	61	

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Table I  
(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of paw volume	ED <sub>50</sub> mg/kg p.o.
Phenylbutazon	25	10	21	
	50	15	42	
	100	15	45	100.9
	200	15	66	
Naproxen	12.5	15	33	
	25	15	49	
	50	15	64	28.7
	100	15	71	
Indomethacin	1	10	28	
	2	10	40	
	4	10	47	4.1
	8	10	64	
	12	10	67	

n = number of the test animals

Table II  
Inhibitory effect on adjuvant induced arthritis on rats

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of the growth of paw volume, on the 21st day
46	25	10	28.1
61	25	10	38.2
62	25	10	40.3

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Table II

(contd.)

Test compound No.	Dose mg/kg p.o.	n	Percental inhibition of the growth of paw volume, on the 21st day
64	25	10	40.6
67	25	10	32.8
69	25	10	35.2
83	25	12	46.7
85	25	12	28.4
107	25	12	17.8
108	25	12	35.2
109	25	12	36.7
110	25	12	32.1
138	25	10	35.2
Phenylbutazon	50	15	18.5
Naproxen	12.5	15	16.8
	25	15	28.4

n = number of the test animals

Table III  
Hot plate test, on mice

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
46	25	7
	50	18
	100	38

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Table III  
(contd.)

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
61	25	20
	50	22
	100	26
62	12.5	17
	25	19
	50	30
	100	38
64	25	17
	50	39
	100	44
69	25	13
	50	24
	100	30
74	25	19
	50	26
	100	43
83	25	16
	50	28
	100	59
107	25	34
	50	41
	100	88
108	25	34
	50	46
	100	46

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Table III  
(contd.)

Test compound No.	Dose mg/kg p.o.	Lengthening of reaction time in %
110	25	21
	50	34
	100	52
138	25	25
	50	37
	100	82
Phenylbutazon	100	29
	150	42
	200	44
Naproxen	12.5	25
	25	31
	50	45
	100	49

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Table IV  
In vitro antifungal effect on Erysiphe graminis  
test organism

Test compound No.	Concentration / <u>ug/ml</u>	Inhibition %	ED <sub>50</sub> / <u>ug/ml</u>
1	37.5	50.6	
	50	72.6	
	75	83.0	
	100	85.3	32.9
	150	86.8	
	200	90.1	
8	400	99.6	
	25	42.1	
	50	70.9	
	100	82.0	
	150	84.1	31.1
	200	91.9	
10	400	98.8	
	25	20.3	
	50	42.8	
	100	76.4	56.9
	200	92.7	
	400	90.1	
6	25	49.2	
	50	71.6	
	100	85.1	27.9
	200	89.5	
	400	99.4	

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Table IV  
(contd.)

Test compound No.	Concentration / $\mu$ g/ml	Inhibition %	ED <sub>50</sub> / $\mu$ g/ml
22	25	40.8	
	50	67.7	
	100	79.8	31.2
	200	93.0	
	400	96.9	
Karathane	12.5	24.9	
	25	46.2	
	50	72.7	27.4
	100	87.9	
Chino in fun- dazol 50 WP	50	55.3	
	100	72.6	41.2
	200	89.1	
	400	94.6	

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Further details of the present invention are to be found in the following Examples without limiting the scope of protection to the said Examples.

5

Example 1

4-(1H-1,2,4-triazole-1-yl)-7-chloro-  
-quinoline

A mixture of 1.98 g of 4,7-dichloro-10 -quinoline, 1.38 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 6 hours, whereupon the reaction mixture is poured into 100 ml of water and neutralized with 1 ml of a concentrated ammonium hydroxide solution. The precipitated product 15 is filtered and recrystallized from ethanol. Thus 1.61 g of the desired product are obtained, yield 70 %, Mp.: 169 - 170 °C.

Example 2

4-(1H-1,2,4-triazole-1-yl)-2,8-dimethyl-  
-quinoline

A mixture of 1.91 g of 2,8-dimethyl-4-chloro-quinoline and 1.38 g of 1,2,4-triazole is melt at 120 °C and stirred for 2 hours. The 25 solidified melt is dissolved in a mixture of ethanol and water. The solution is poured into a solution of 0.84 g of sodium bicarbonate and 20 ml of water. The precipitated product is filtered. Thus 1.97 g of the desired compound are obtained, yield 88 %, m.p.: 30 99 - 100 °C.

Example 3

4-(1H-1,2,4-triazole-1-yl)-2-methyl-6-  
-methoxy-quinoline

35 A mixture of 2.44 g of 2-methyl-4-chloro-

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-6-methoxy-quinoline-hydrochloride, 1.38 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 80 °C for 3 hours whereupon the reaction mixture is poured into 100 ml of water and 5 neutralized with 2 ml of a concentrated ammonium hydroxide solution. The precipitated product is filtered. Thus 2.09 g of the desired compound are obtained, yield 87 %, mp.: 117 - 118 °C.

10

Example 4

4-(1H-1,2,4-triazole-1-yl)-2-methyl-6,8-dichloro-quinoline

A mixture of 2.46 g of 2-methyl-4,6,8-trichloro-quinoline, 1.82 g of the sodium salt 15 of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 25 hours whereupon the reaction mixture is poured into 100 ml of water. The precipitated product is filtered. Thus 2.59 g of the desired compound are obtained, yield 93 %.  
20 Mp.: 220 - 222 °C.

25

Example 5

4-(1H-1,2,4-triazole-1-yl)-2,8-bis-trifluoromethyl-quinoline

A mixture of 3.0 g of 4-chloro-2,8-bis-trifluoromethyl-quinoline, 1.38 g of 1,2,4-triazole, 1.38 g of potassium carbonate and 30 ml of acetone is heated to boiling for 23 hours whereupon the reaction mixture is poured into 100 ml of water. The precipitated product is filtered, dissolved in 5 ml of ethanol, whereupon 5 ml of water are added. The precipitated product is filtered. Thus 2.42 g of the desired compound are obtained, yield: 73 %, mp.: 106 - 107 °C.

35

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Example 6

4-[1H-1,2,4-triazole-3(5)-yl-5(3)-  
-mercapto]-2-trichloromethyl-8-chloro-  
quinoline

5 A mixture of 3.16 g of 2-trichloromethyl-  
-4,8-dichloro-quinoline, 1.48 g of the sodium salt  
of 3(5)-mercapto-1,2,4-triazole and 10 ml dimethyl-  
formamide is stirred at 100 °C for 18 hours. The  
reaction having been completed the reaction mixture  
10 is poured into water, the precipitated product is  
filtered and recrystallized from ethanol. Thus 2.1 g  
of the desired compound are obtained, yield 55 %,  
M.p.: 188 - 183 °C.

15

Example 7

4-[5(3)-ethyl-1H-1,2,4-triazole-3(5)-yl-  
-mercapto]-2,8-dimethyl-quinoline

A mixture of 1.32 g of 4-chloro-2,8-di-  
methyl-quinoline, 1.55 g of 3(5)-mercapto-5(3)-  
20 -ethyl-1,2,4-triazole and 20 ml of ethanol is  
stirred at 30 °C for 20 hours. The reaction mixture  
is poured into 50 ml of water, neutralized with  
1 ml of concentrated ammonium hydroxide and the  
precipitated product is filtered. Thus 2.41 g of  
25 the desired compound are obtained, yield 85 %,  
mp.: 176 - 177 °C.

30

Example 8

2-(1H-1,2,4-triazole-1-yl)-3-methyl-  
-quinoline

A mixture of 1.78 g of 2-chloro-3-methyl-  
-quinoline and 0.69 g of 1,2,4-triazole is melt and  
allowed to stand at 120 °C for 4 hours. The melt is  
cooled, then dissolved in 10 ml of ethanol, poured  
35 into 20 ml of water and neutralized with 1 ml of

- 25 -

concentrated ammonium hydroxide. The precipitated product is filtered. Thus 1.49 g of the desired compound are obtained, yield 71 %. Mp.: 80 - 81 °C.

5

Example 9

2-(1H-1,2,4-triazole-1-yl)-4-methyl-  
-quinoline hydrochloride

A mixture of 1.78 g of 2-chloro-4-methyl-quinoline, 0.76 g of 1,2,4-triazole and 10 ml of chloro benzene is stirred at 100 °C for 7 hours. The reaction mixture is cooled, the precipitated product is filtered, dissolved in 5 ml of ethanol and precipitated by adding 10 ml of ethyl ether. The precipitated product is filtered. Thus 1.72 g of the desired compound are obtained, yield 70 %. Mp.: 193 - 194 °C.

20

Example 10

2-(1H-1,2,4-triazole-1-yl)-7-chloro-3,8-  
-dimethyl-quinoline

A mixture of 2.26 g of 2,7-dichloro-3,8-dimethyl-quinoline, 1,1 g of the sodium salt of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 25 hours. The reaction mixture is poured into 100 ml of water and the precipitated product is filtered. Thus 2.48 g of the desired compound are obtained, yield 96 %. Mp.: 147 - 148 °C.

30

Example 11-

2-(3-methyl-1H-1,2,4-triazole-1-yl)-4,6-  
-bis-trichloromethyl-quinoline

A mixture of 3.99 g of 2-chloro-4,6-bis-trichloromethyl-quinoline, 1.26 g of the sodium salt of 3-methyl-1,2,4-triazole and 10 ml of dimethyl

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formamide is stirred at 100 °C for 20 hours. The reaction mixture is poured into 100 ml of water, the precipitated product is filtered and recrystallized from 10 ml of ethanol. Thus 2.76 g of 5 the desired compound are obtained, yield 62 %.  
M.p.: 169 - 170 °C.

Example 12

2-[5(3)-methyl-1H-1,2,4-triazole-3(5)-y1-mercaptop]-3-methyl-quinoline-hydrochloride

10 A mixture of 1.78 g of 2-chloro-3-methyl-quinoline, 1.38 g of 3(5)-mercaptop-5(3)-methyl-1,2,4-triazole and 10 ml of chloro benzene is 15 stirred at 100 °C for 2 hours. The reaction mixture is cooled, the precipitated product is filtered and washed with diethyl ether. Thus 2.8 g of the desired compound are obtained, yield 96 %, mp.: 190 - 192 °C.

20

Example 13

2-[1H-1,2,4-triazole-3(5)-y1-mercaptop]-4,8-dimethyl-quinoline-hydrochloride

25 A mixture of 1.92 g of 2-chloro-4,8-dimethyl-quinoline and 1.21 g of 3(5)-mercaptop-1,2,4-triazole is melt and allowed to stand at 120 °C for an hour. The cooled reaction mixture is treated with 5 ml of hot ethanol, cooled and filtered. Thus 1.90 g of the desired compound are obtained, yield 65 %. Mp.: 201 - 202 °C.

30

Example 14

4-(1H-1,2,4-triazole-1-y1)-2,8-dimethyl-5-chloro-quinoline

35 A mixture of 2.26 g of 4,5-dichloro-2,8-dimethyl-quinoline, 1.38 g of 1,2,4-triazole and

- 27 -

0.1 g of 96 % sulfuric acid is stirred at 70 °C for 3 hours. The reaction mixture is poured into 50 ml of water and neutralized with 1 ml of a concentrated ammonium hydroxide solution. The precipitated 5 product is filtered and washed with water. Thus 2.0 g of the desired compound are obtained, yield 77.4 %. Mp.: 117-118 °C.

Example 15

10 4-[5(3)-methyl-1H-1,2,4-triazole-3(5)-  
-yl-mercaptop]-2-methyl-7,8-dichloro-  
-quinoline

A mixture of 2.46 g of 2-methyl-4,7,8-trichloro-quinoline, 1.38 g of 3(5)-mercaptop-5(3)-15 -methyl-1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 8 hours. The reaction mixture is poured into 100 ml of water, neutralized and the precipitated product is filtered. Thus 3.10 g of the desired compound are obtained, yield 95 %.  
20 Mp.: 156 - 158 °C.

Example 16

2-(1H-1,2,4-triazole-1-yl)-3-methyl-  
-7-ethyl-quinoline

25 A mixture of 2.05 g of 2-chloro-3-methyl-7-ethyl-quinoline, 1.05 g of 1,2,4-triazole-hydrochloride, 0.69 g of 1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 100 °C for 6 hours. The reaction mixture is poured into 100 ml 30 of water, neutralized and the crude product is recrystallized from a mixture of ethanol and hexane. Thus 1.52 g of the desired compound are obtained, yield 64 %. Mp.: 72 - 73 °C.

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Example 17

2-[1H-1,2,4-triazole-3(5)-yl-mercaptopo]-  
-4-methyl-quinoline

A mixture of 1.78 g of 2-chloro-4-methyl-quinoline, 1.21 g of 3(5)-mercaptopo-1,2,4-triazole and 10 ml of dimethyl formamide is stirred at 40 °C for 3 hours. The reaction mixture is poured into 100 ml of water, neutralized and filtered. Thus 2.37 g of the desired compound are obtained, yield 98 %, m.p.: 96 - 98 °C.

Example 18

3-[5(3)-ethyl-1H-1,2,4-triazole-3(5)-yl-mercaptopo]-3,8-dimethyl-quinoline

1.91 g of 2-chloro-3,8-dimethyl-quinoline and 1.55 g of 3(5)-mercaptopo-5(3)-ethyl-1,2,4-triazole are reacted in an analogous manner to Example 16. The crude product is recrystallized from a mixture of chloroform and ethanol. Thus 1.93 g of the desired compound are obtained, yield 68 %. Mp.: 190 - 192 °C.

Further compounds are prepared in an analogous manner to the process described in the preceding Examples. The compounds are disclosed in the following Table V. The number appearing in the column "method" relates to the number of the Example used for the preparation of the compound in caption.

Table V  
Compounds of the General Formula (Ia)

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Method	Yield (%)	Mp. °C
1	H	7-Cl	H	H	1	70	169-170
2	H	8-CH <sub>3</sub>	H	H	1	81	142-144
3	H	8-CF <sub>3</sub>	H	H	4	75	146-147
4	2-CH <sub>3</sub>	H	H	H	3	57	88-89
5	2-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	3	71	110-112
6	2-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H	1	88	98-100
7	2-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H	3	87	117-118
8	2-CH <sub>3</sub>	8-OCH <sub>3</sub>	H	H	3	68	179-180
9	2-CH <sub>3</sub>	6-Cl	H	H	3	58	173-175
10	2-CH <sub>3</sub>	8-Cl	H	H	4	97	142-144
11	2-CH <sub>3</sub>	7-CF <sub>3</sub>	H	H	4	93	68-70
12	2-CH <sub>3</sub>	8-CF <sub>3</sub>	H	H	4	86	154-156

13	2-CH <sub>3</sub>	6-OH	H	H	1	40	238-240
14	2-CH <sub>3</sub>	6-COCH <sub>3</sub>	H	H	1	28	169-190
15	2-CH <sub>3</sub>	7-COOCH <sub>3</sub>	H	H	1	49	184-186
16	2-CH <sub>3</sub>	8-CH	H	H	4	57	208-210
17	2-CH <sub>3</sub>	5-Cl	8-CH <sub>3</sub>	H	1	88	113-115
18	2-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	H	4	50	173-175
19	2-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	H	4	98	147-149
20	2-CH <sub>3</sub>	5-Cl	8-Cl	H	1	74	123-124
21	2-CH <sub>3</sub>	6-Cl	8-Cl	H	4	93	220-222
22	2-CH <sub>3</sub>	7-Cl	8-Cl	H	4	93	168-170
23	2-CH <sub>3</sub>	5-Cl	8-OCH <sub>3</sub>	H	1	59	188-190
24	2-CH <sub>3</sub>	5-CH <sub>3</sub>	7-CH <sub>3</sub>	H	1	59	119-121
25	2-CH <sub>3</sub>	5-CH <sub>3</sub>	8-CH <sub>3</sub>	H	1	64	120-122
26	2-CH <sub>3</sub>	6-CH <sub>3</sub>	8-CH <sub>3</sub>	H	1	66	129-131

27	2-CH <sub>3</sub>	7-CH <sub>3</sub>	8-CH <sub>3</sub>	H	1	62	128-130
28	2-CH <sub>3</sub>	5-CH <sub>3</sub>	8-NHCOCH <sub>3</sub>	H	1	57	232-234
29	2-CH <sub>3</sub>	5-CH <sub>3</sub>	8-NH <sub>2</sub>	H	1	35	205-207
30	2-CCl <sub>3</sub>	6-CH <sub>3</sub>	H	H	4	50	102-104
31	2-CCl <sub>3</sub>	8-CH <sub>3</sub>	H	H	4	61	130-132
32	2-CCl <sub>3</sub>	8-OCH <sub>3</sub>	H	H	4	31	169-170
33	2-CCl <sub>3</sub>	8-Cl	H	H	5	40	133-135
34	2-CCl <sub>3</sub>	6-CCl <sub>3</sub>	H	H	5	47	162-163
35	2-CCl <sub>3</sub>	8-CCl <sub>3</sub>	H	H	5	50	157-158
36	2-CCl <sub>3</sub>	8-CF <sub>3</sub>	H	H	5	47	132-133
37	2-CCl <sub>3</sub>	6-Cl	8-Cl	H	5	73	157-159
38	2-CF <sub>3</sub>	8-CF <sub>3</sub>	H	H	5	73	106-107
-	-	-	-	-	-	-	-

Compound of the General Formula (Ib)

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Method	Yield (%)	M.p. °C
39	H	7-Cl	H	H	7	77	161-162
40	2-CH <sub>3</sub>	H	H	H	7	66	181-182
41	2-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	7	59	167-169
42	2-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H	7	71	143-145
43	2-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H	7	98	191-192
44	2-CH <sub>3</sub>	8-OCH <sub>3</sub>	H	H	7	77	186-187
45	2-CH <sub>3</sub>	6-Cl	H	H	7	68	194-195
46	2-CH <sub>3</sub>	8-Cl	H	H	7	88	199-200
47	2-CH <sub>3</sub>	7-CF <sub>3</sub>	H	H	7	76	205-207
48	2-CH <sub>3</sub>	8-CF <sub>3</sub>	H	H	7	42	183-184
49	2-CH <sub>3</sub>	5-Cl	8-CH <sub>3</sub>	H	7	78	184-186
50	2-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	H	7	66	197-199

51	2-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	H	7	79	168-170
52	2-CH <sub>3</sub>	6-Cl	8-Cl	H	7	65	206-207
53	2-CH <sub>3</sub>	7-Cl	8-Cl	H	7	87	199-200
54	2-CCl <sub>3</sub>	6-CH <sub>3</sub>	H	H	15	72	127-129
55	2-CCl <sub>3</sub>	8-CH <sub>3</sub>	H	H	6	40	166-168
56	2-CCl <sub>3</sub>	8-Cl	H	H	6	55	188-189
57	2-CCl <sub>3</sub>	8-CCl <sub>3</sub>	H	H	6	18	129-130
58	2-CCl <sub>3</sub>	8-CF <sub>3</sub>	H	H	6	50	190-192
59	2-CCl <sub>3</sub>	6-Cl	8-Cl	H	6	48	214-215
60	2-CF <sub>3</sub>	8-CF <sub>3</sub>	H	H	6	24	208-210
61	H	7-Cl	H	CH <sub>3</sub>	7	65	227-228
62	2-CH <sub>3</sub>	H	H	CH <sub>3</sub>	15	82	175-177
63	2-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	15	78	181-182
64	2-CH <sub>3</sub>	8-CH <sub>3</sub>	H	CH <sub>3</sub>	15	85	198-200

65	2-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	OH <sub>3</sub>	15	98	192-193
66	2-CH <sub>3</sub>	8-OCH <sub>3</sub>	H	CH <sub>3</sub>	15	98	186-187
67	2-CH <sub>3</sub>	8-CF <sub>3</sub>	H	CH <sub>3</sub>	15	96	180-182
68	2-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	CH <sub>3</sub>	15	99	207-208
69	2-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	CH <sub>3</sub>	15	62	191-193
70	2-CH <sub>3</sub>	6-Cl	8-Cl	CH <sub>3</sub>	15	38	209-211
71	2-CH <sub>3</sub>	7-Cl	8-Cl	CH <sub>3</sub>	15	95	156-158
72	H	7-Cl	H	CH <sub>2</sub> CH <sub>3</sub>	7	79	154-156
73	2-CH <sub>3</sub>	H	H	CH <sub>2</sub> CH <sub>3</sub>	7	44	135-137
74	2-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	7	36	171-172
75	2-CH <sub>3</sub>	8-ClI <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	7	85	176-177
76	2-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	15	77	168-170
77	2-CH <sub>3</sub>	8-OCH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	7	30	171-173
78	2-CH <sub>3</sub>	8-CF <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	15	81	162-165



## Compounds of the General Formula (Ic)

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Method	Yield (%)	N <sub>P</sub> C
83	3-CH <sub>3</sub>	H	H	H		16	71
84	3-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H		16	68
85	3-CH <sub>3</sub>	7-CH <sub>3</sub>	H	H		16	88-90
86	3-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H		10	87
87	3-CH <sub>3</sub>	6-CH <sub>2</sub> CH <sub>3</sub>	H	H		16	30
88	3-CH <sub>3</sub>	7-CH <sub>2</sub> CH <sub>3</sub>	H	H		16	99-101
89	3-CH <sub>3</sub>	8-CH <sub>2</sub> CH <sub>3</sub>	H	H		16	58
90	3-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H		16	81-83
91	3-CH <sub>3</sub>	6-Cl	H	H		16	72-73
92	3-CH <sub>3</sub>	7-Cl	H	H		10	41
93	3-CH <sub>3</sub>	5-CH <sub>3</sub>	7-CH <sub>3</sub>	H		16	79-80
94	3-CH <sub>3</sub>	6-CH <sub>3</sub>	7-CH <sub>3</sub>	H		16	87-89
							117-115

95	3-CH <sub>3</sub>	5-CH <sub>3</sub>	8-CH <sub>3</sub>	H	16	51	138-140
96	3-CH <sub>3</sub>	6-CH <sub>3</sub>	8-CH <sub>3</sub>	H	16	84	126-128
97	3-CH <sub>3</sub>	7-CH <sub>3</sub>	8-CH <sub>3</sub>	H	16	76	118-119
98	3-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	H	10	90	194-195
99	3-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	H	10	96	147-148
100	4-CH <sub>3</sub>	H	H	H	16	99	111-113
101	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	16	71	134-136
102	4-CH <sub>3</sub>	7-CH <sub>3</sub>	H	H	10	66	134-135
103	4-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H	10	63	124-126
104	4-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H	10	71	124-126
105	4-CH <sub>3</sub>	7-Cl	H	H	10	66	193-195
106	4-CCl <sub>3</sub>	6-CCl <sub>3</sub>	H	CH <sub>3</sub>	11	62	169-170
-	-	-	-	-	-	-	-

Compounds of the General Formula (Ia)

Compound No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Method	Yield (%)	N.P. %
107	3-CH <sub>3</sub>	H	H	H	17	62	144-145
108	3-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	17	84	165-166
109	3-CH <sub>3</sub>	7-CH <sub>3</sub>	H	H	17	99	170-171
110	3-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H	18	60	124-125
111	3-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H	18	51	158-160
112	3-CH <sub>3</sub>	6-Cl	H	H	17	80	180-190
113	3-CH <sub>3</sub>	7-Cl	H	H	17	80	213-215
114	3-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	H	18	60	19-192
115	3-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	H	18	68	205-206
116	4-CH <sub>3</sub>	H	H	H	17	98	96-98
117	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	H	18	92	125-126
118	4-CH <sub>3</sub>	7-CH <sub>3</sub>	H	H	18	74	134-136

119	4-CH <sub>3</sub>	8-CH <sub>3</sub>	H	H	18	50	135-137
120	4-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	H	18	81	152-154
121	4-CH <sub>3</sub>	7-Cl	H	H	18	83	158-160
122	3-CH <sub>3</sub>	H	H	CH <sub>3</sub>	17	84	211-212
123	3-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	18	74	215-216
124	3-CH <sub>3</sub>	7-CH <sub>3</sub>	H	CH <sub>3</sub>	17	85	204-205
125	3-CH <sub>3</sub>	8-CH <sub>3</sub>	H	CH <sub>3</sub>	18	74	212-213
126	3-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	CH <sub>3</sub>	18	72	205-207
127	3-CH <sub>3</sub>	6-Cl	H	CH <sub>3</sub>	18	79	213-215
128	3-CH <sub>3</sub>	7-Cl	H	CH <sub>3</sub>	18	74	205-206
129	3-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	CH <sub>3</sub>	18	40	226-227
130	3-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	CH <sub>3</sub>	18	87	228-230
131	4-CH <sub>3</sub>	H	H	CH <sub>3</sub>	17	78	172-174
132	4-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>3</sub>	17	74	189-190

133	4-CH <sub>3</sub>	7-CH <sub>3</sub>	H	CH <sub>3</sub>	18	59	172-174
134	4-CH <sub>3</sub>	8-CH <sub>3</sub>	H	CH <sub>3</sub>	18	67	188-190
135	4-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	CH <sub>3</sub>	17	86	192-193
136	4-CH <sub>3</sub>	7-Cl	H	CH <sub>3</sub>	17	79	179-180
137	3-CH <sub>3</sub>	H	H	CH <sub>2</sub> CH <sub>3</sub>	17	85	187-189
138	3-CH <sub>3</sub>	6-CH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	18	68	209-211
139	3-CH <sub>3</sub>	7-CH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	17	57	145-146
140	3-CH <sub>3</sub>	8-CH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	18	68	190-192
141	3-CH <sub>3</sub>	6-OCH <sub>3</sub>	H	CH <sub>2</sub> CH <sub>3</sub>	17	67	192-195
142	3-CH <sub>3</sub>	6-Cl	H	CH <sub>2</sub> CH <sub>3</sub>	18	67	203-205
143	3-CH <sub>3</sub>	7-Cl	H	CH <sub>2</sub> CH <sub>3</sub>	17	73	191-193
144	3-CH <sub>3</sub>	6-Cl	8-CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	18	50	185-186
145	3-CH <sub>3</sub>	7-Cl	8-CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	18	72	214-215
146	4-CH <sub>3</sub>	H	H	CH <sub>2</sub> CH <sub>3</sub>	17	92	130-131

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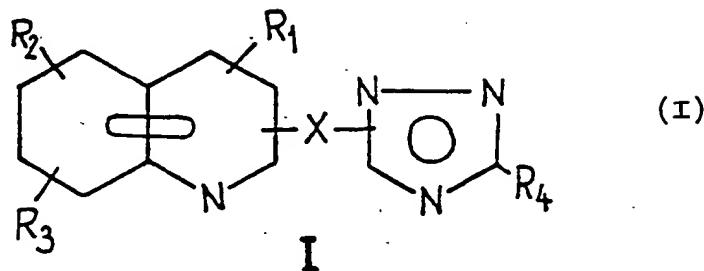
- 42 -

What we claim is:

1. Triazolyl quinoline derivatives of  
the general Formula (I)

5

10



(wherein

15      R<sup>1</sup>      stands for hydrogen, methyl, trihalogeno-  
methyl or carboxy;

20      R<sup>2</sup>      is hydrogen, halogen, C<sub>1-4</sub> alkyl, hydroxy,  
C<sub>1-4</sub> alkoxy, phenoxy, amino, acetamino,  
C<sub>1-4</sub> dialkylamino, acetyl, benzoyl,  
methylthio, carboxy, cyano, ethoxycar-

25      R<sup>3</sup>      bonyl, nitro or trihalogenomethyl;  
represents hydrogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub>

30      R<sup>4</sup>      alkoxy;

35      X      stands for hydrogen, methyl or ethyl and  
stands for a valency bond or -S- )

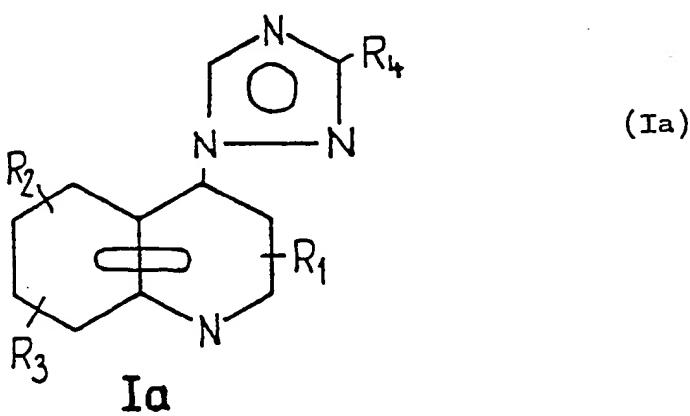
40      and acid addition salts thereof.

2. Compounds according to Claim 1 of the  
45      general Formula (Ia)

30

35

(Ia)



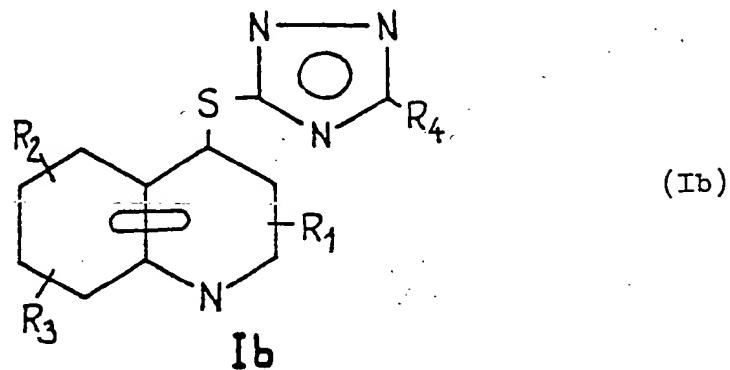
- 43 -

(wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as stated in Claim 1) and acid addition salts thereof.

3. Compounds according to Claim 1 of the general Formula (Ib)

5

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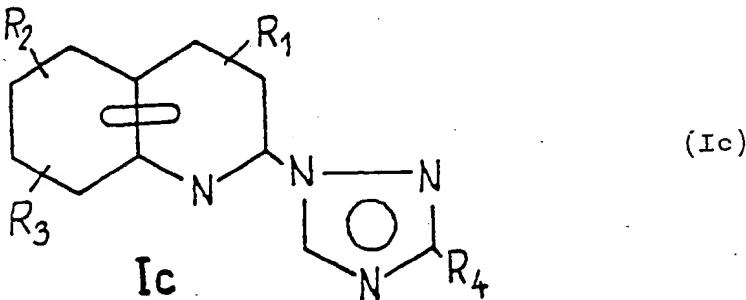


15 (wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as stated in Claim 1) and acid addition salts thereof.

4. Compounds according to Claim 1 of the general Formula (Ic)

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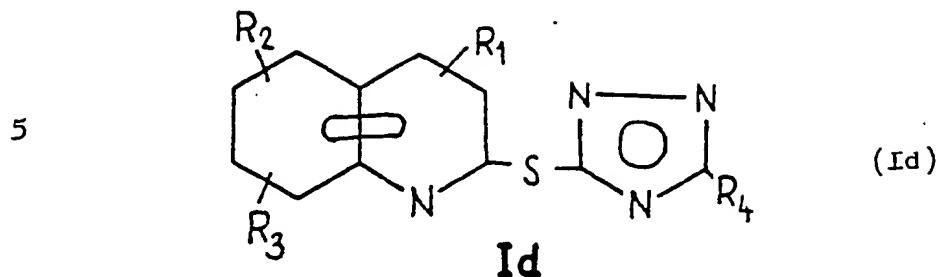
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wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as stated in Claim 1) and acid addition salts thereof.

30 5. Compounds according to Claim 1 of the general Formula (Id)

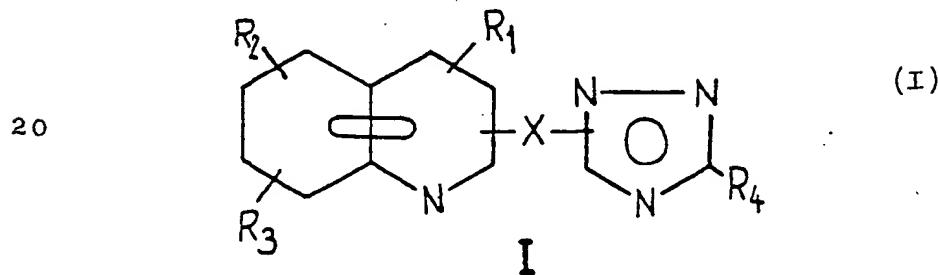
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(wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as stated in Claim 1) and acid addition salts thereof.

6. A process for the preparation of  
15 triazolyl quinoline derivatives of the general  
Formula (I)



(wherein

25  $R^1$  stands for hydrogen, methyl, trihalogeno-methyl or carboxy;

$R^2$  stands for hydrogen, halogen,  $C_{1-4}$  alkyl, hydroxy,  $C_{1-4}$  alkoxy, phenoxy, amino, acetamino,  $C_{1-4}$  dialkylamino, acetyl,

30                   benzoyl, methylthio, carboxy, cyano,  
                 ethoxycarbonyl, nitro or trihalogeno-  
                 methyl;

$R^3$  represents hydrogen,  $C_{1-4}$  alkyl or  $C_{1-4}$  alkoxy;

35  $R^4$  stands for hydrogen, methyl or ethyl and

- 45 -

X stands for a valency bond or -S-)  
 and acid addition salts thereof which comprises  
 reacting a halogeno quinoline derivative of the  
 general Formula (II)

5

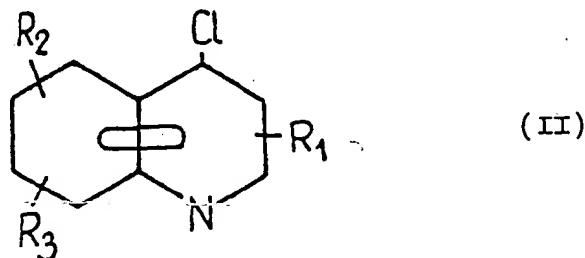
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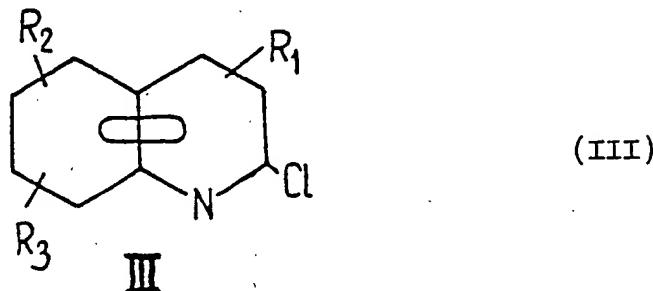
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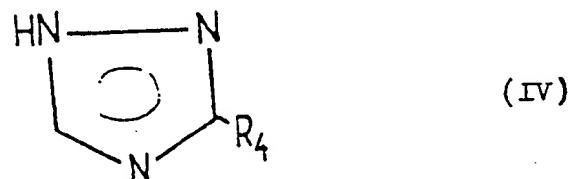


or (III)

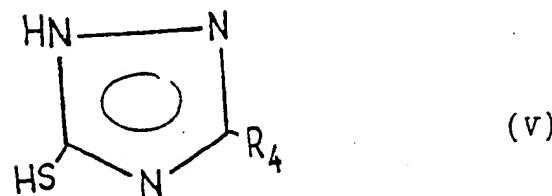
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(wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as stated above) with  
 a 1,2,4-triazole of the general Formula (IV)



30 or (V)



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(wherein R<sup>4</sup> is as stated above) in the presence or absence of a solvent, in the presence or absence of an acid or a base, at a temperature between 0 °C and 200 °C and if desired, isolating 5 the product thus obtained in the form of the free base or an acid addition salt thereof.

7. A process according to Claim 6 for the preparation of compounds of the general Formula (Ia) which comprises reacting a 4-chloro-10 -quinoline derivative of the general Formula (II) with a 1,2,4-triazole of the general Formula (IV) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated in Claim 6).

8. A process according to Claim 6 for 15 the preparation of compounds of the general Formula (Ib) which comprises reacting a 4-chloro-quinoline derivative of the general Formula (II) with a 3-mercaptop-1,2,4-triazole of the general Formula (V) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as 20 stated in Claim 6.).

9. A process according to Claim 6 for the preparation of compounds of the general Formula (Ic) which comprises reacting a 2-chloro-quinoline of the general Formula (III) with a 25 1,2,4-triazole of the general Formula (IV) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated in Claim 6).

10. A process according to Claim 6 for the preparation of compounds of the general Formula (Id) which comprises reacting a 2-chloro-30 -quinoline derivative of the general Formula (III) with a 3-mercaptop-1,2,4-triazole of the general Formula (V) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as stated in Claim 6.).

11. Pharmaceutical compositions comprising 35 in an effective amount at least one compound of the

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general Formula (I) (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as stated in Claim 1) or a pharmaceutically acceptable acid addition salt thereof as active ingredient in admixture with suitable inert solid 5 or liquid pharmaceutical carriers.

12. A process for the preparation of pharmaceutical compositions according to Claim 11 which comprises admixing at least one compound of the general Formula (I) or a pharmaceutically acceptable acid addition salt thereof with suitable inert solid or liquid pharmaceutical carriers. 10

13. Fungicidal compositions comprising as active ingredient in an effective amount at least one compound of the general Formula (I) 15 (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as stated in Claim 1) or an acid addition salt thereof in admixture with suitable inert solid or liquid carriers or diluents.

14. A process for the preparation 20 of fungicidal compositions according to Claim 13 which comprises admixing at least one compound of the general Formula (I) or an acid addition salt thereof with suitable inert solid or liquid carriers or diluents.

25 15. A method for combating fungal diseases which comprises applying an effective amount of a fungicidal composition according to Claim 13 onto the plants, parts or environment thereof or the pests or the objects to be protected.

30 16. Compounds of the general Formula (I) and acid addition salts thereof whenever prepared by the process according to any of Claims 6-10.

17. A process as substantially disclosed herein with particular reference to the Examples.

# INTERNATIONAL SEARCH REP RT

International Application No PCT/HU 86/00026

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC  
 IPC : C 07 D 401/04, 401/12, //A 01 N 43/653, A 61 K 31/47,  
 (C 07 D 401/04, 249:08, 215:12) (C 07 D 401/12, 249:08, 215:36)

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
Int.Cl. <sup>4</sup>	C 07 D 401/04, 401/12

Documentation Searched other than Minimum Documentation  
 to the Extent that such Documents are Included in the Fields Searched \*

AT

## III. DOCUMENTS CONSIDERED TO BE RELEVANT\*

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages 13	Relevant to Claim No. 13
X	Chemical Abstracts, vol. 99, no. 17, issued October 24, 1983 (Columbus, Ohio, USA), E. G. KNYSH "Synthesis and biological activity of some 5-hetarylmercapto-1,2,4-triazoles", see page 592, column 1, abstract-no. 139 866z, Khim.-Form. Zh, 1983 17(7), 798-801 (Russ).	(1)
X	DE, A, 2 147 794 (MERCK) 30 March 1972 (30.03.72), see claim 1, page 4, lines 9-18.	(1,11)
A	Chemical Abstracts, vol. 94, no. 25, issued June 22, 1981 (Columbus, Ohio, USA), M. YOSHIDA "8-Quinolinesulfonyl tetrazolide as a coupling agent for oligonucleotides synthesis via triester approach", see page 631, column 2, abstract-no. 209 126f, Chiba Kogyo Daigaku Kenkyu Hokoku, Riko-hen 1980, 25, 53-9 (Japan).	(1)

\* Special categories of cited documents: \*\*

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

23 June 1986 (23.06.86)

Date of Mailing of this International Search Report

25 June 1986 (25.06.86)

International Searching Authority

AUSTRIAN PATENT OFFICE

Signature of Authorized Officer

## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SEC ND SHEET)

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, vol. 83, no. 23, issued December 8, 1975 (Columbus, Ohio, USA), J. J. BALDWIN "4-Trifluoromethylimidazoles and 5-(4-pyridyl)-1,2,4-triazoles, new classes of xanthine oxidase inhibitors", see page 14, column 1, abstract-no. 188 199n, J. Med. Chem. 1975, 18(9), 895-900 (Eng).	(1)
A	Chemical Abstracts, vol. 98, no. 17, issued April 25, 1983 (Columbus, Ohio, USA), P.K. KADABA "Triazolines", see page 572, column 2, abstract-no. 143 336y, J. Prakt. Chem. 1982, 324(5), 857-64 (Eng).	(1)
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Anhang zum internatio-  
nalen Recherchenbericht  
über die internationale  
Patentanmeldung  
Nr.

In diesem Anhang sind  
die Mitglieder der  
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obengenannten interna-  
tionalen Recherchenbe-  
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Patentdokumente ange-  
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Annex to the International  
Search Report on Interna-  
tional Patent Application  
No. PCT/HU 86/00026

This Annex lists the patent  
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the patent documents cited  
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Im Recherchenbericht angeführtes Patent- dokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum : Veröffentlichung Publication date Date de publication
DE-A-2 147 794	30/03/1972	AU-A1- 33 427/71 BE-A1- 781 055 CA-A1- 950 463 CH-A - 562 813 FR-A5- 2 107 984 FR-B1- 2 107 984 GB-A - 1 358 893 JP-B4-49-046 622 NL-A - 7 112 373 US-A - 3 865 945 US-A - 3 879 404 US-A - 4 011 218 US-A - 4 071 518 US-A - 4 102 889 US-A - 4 156 085 US-A - 4 198 513 US-A - 4 256 887	22/03/1971 22/09/1971 02/07/1971 13/06/1971 12/05/1971 01/08/1971 03/07/1971 11/12/1971 28/03/1971 11/02/1971 22/04/1971 08/03/1971 31/01/1971 25/07/1971 22/05/1971 15/04/1971 17/03/1981